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Perioperative Use of Eicosapentaenoic Acid and Patency of Infrainguinal Vein Bypass: A Retrospective Chart Review

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ABSTRACT

Background: A significant proportion of autogenous vein grafts fail in the long term. Currently, there is no treatment to improve graft patency.

Objective: This study was designed to assess the effectiveness of eicosapentaenoic acid (EPA) to prevent late failure of an autogenous vein graft and other perioperative risk factors affecting long-term patency.

Methods: A retrospective chart review was performed on grafts of patients who underwent infrainguinal bypass surgery using autogenous vein grafts for peripheral arterial disease in a lower limb. Patients were stratified by the perioperative use of EPA. The EPA group was those patients who administered EPA ≥1 time within 3 months of surgery. The non-EPA group was made up of those patients who did not administer EPA within 3 months of surgery. Primary, assisted primary, and secondary patency rates of the grafts in each group were calculated by the Kaplan-Meier method and compared by the log-rank test. To evaluate the effect of other perioperative risk factors, a Cox proportional hazards analysis was performed.

Results: One hundred sixty-one grafts were analyzed from 159 patients who underwent surgery between July 1991 and July 2005. The primary patency rates of the EPA and non-EPA groups were 93% and 86%, 89% and 74%, and 83% and 68% at 1, 3, and 5 years, respectively. In terms of primary patency, the EPA group was significantly better than the non-EPA group ($P = 0.042$). There was no significant difference between the groups in either assisted primary or secondary patency. A Cox proportional hazard analysis found that the minimum graft diameter and perioperative use of EPA were significant factors for primary patency ($P = 0.002$ and $P = 0.004$, respectively). Graft diameter was the only significant factor for assisted primary and secondary patency ($P = 0.021$ and $P = 0.003$, respectively).

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Conclusion: Although graft diameter was the most important factor for long-term patency of infrainguinal vein bypass grafts, the perioperative use of EPA significantly improved primary patency among these subjects. (*Curr Ther Res Clin Exp.* 2007;68:161–174)

Key words: eicosapentaenoic acid, graftpatency, autogenous vein graft, long-term outcome, perioperative use.

INTRODUCTION

Use of an autogenous vein is the gold standard for infrainguinal bypass.[1] However, 20% to 30% of implanted autogenous vein grafts fail in the long term after bypass surgery.[2] The problems that occur between 2 and 18 months are usually attributed to intimal hyperplasia; thereafter, changes are primarily due to the progression of atherosclerosis.[3,4] Accordingly, prevention of intimal hyperplasia might improve the long-term patency of autogenous vein grafts.

Eicosapentaenoic acid (EPA), an agent contained in fish oil, is well known for its action against arteriosclerosis by replacing arachidonic acid in the lipopolysaccharides of the cell membrane.[5,6] Clinical and experimental trials have suggested antiatherogenic and antithrombotic effects for EPA, including benefits on lipoprotein metabolism, blood pressure, endothelial function, vascular reactivity, inflammation, platelet and fibrinolytic function, cytokine production, coagulation, and oxidative stress.[7,8] Because these events can influence the development of intimal hyperplasia in an implanted autogenous vein graft, oral administration of EPA in the perioperative period might prevent late failure of autogenous vein grafts.

The purpose of this study was to assess the effectiveness of perioperative EPA on the long-term outcome of autogenous vein bypass for peripheral arterial disease, and to elucidate the perioperative risk factors affecting graft patency.

MATERIALS AND METHODS

The institutional review board of the Nippon Steel Yawata Memorial Hospital, Kitakyushu-City, Japan, approved the study design.

The clinical records of patients who underwent infrainguinal bypass surgery using autogenous vein grafts for peripheral arterial disease in a lower limb were reviewed. These records were obtained from the hospital's computer database. The grafts were categorized into 2 groups depending on perioperative use of EPA. The EPA group started oral EPA (Epadel, Mochida Pharmacuetical Co., Ltd., Tokyo, Japan), 900 to 1800 mg, within 2 weeks after bypass surgery and continued for ≥3 months; the non-EPA group did not take EPA within 3 months after bypass surgery. The grafts of patients who stopped oral EPA within 3 months after surgery, or who started oral EPA >2 weeks after surgery, were excluded. Grafts that occluded within 3 months after surgery regardless of continued use of EPA from the early postoperative period were included in the EPA group.

To elucidate other perioperative risk factors, the following data were noted from the charts: age, sex, diagnosed disease requiring bypass surgery, preoperative complication of diabetes, hypertension, coronary artery disease, stroke, hemodialysis, hypercholesterolemia, smoking history (self-reported), medical records from treating physicians or laboratory data of preoperative examination, operative indication (claudication vs critical limb ischemia), graft orientation (single vein graft vs complex spliced vein graft), distal anastomotic level (popliteal artery vs crural artery or foot artery), number of bypass procedures in ipsilateral limb (first case vs repeat case), concomitant inflow reconstruction, postoperative use of warfarin sodium, antiplatelet therapy (ticlopidine, cilostazol, aspirin, or sarpogrelate hydrogen chloride), statins, postoperative smoking, and graft minimum diameter measured on an angiogram taken 2 to 4 weeks after bypass surgery.

Graft patency was determined objectively by pulsation of the graft, ankle brachial pressure index (ABPI), or color Doppler examination at intervals of 3 months. Investigators were blinded to patient information except with regard to the bypass site. Angiography was recommended in cases of disappearance of graft pulsation, decline of ABPI to 80% of previous levels, or obvious stenosis detected by color Doppler examination. When significant problems leading to graft failure were found with angiography, revision surgery was recommended. The definition of patency was in accordance with the recommended reporting standards of the Ad Hoc Committee on Reporting Standards, Society for Vascular Surgery/North American Chapter, International Society for Cardiovascular Surgery.[9] *Primary patency rate* was defined as the uninterrupted duration of patency without intervention. *Assisted primary patency rate* was defined as uninterrupted duration of patency with intervention. *Secondary patency rate* was defined as duration of patency restored to the same conduit after bypass graft occlusion. The cutoff for follow-up was at 60 months after initial bypass surgery, with the final follow-up undertaken in January 2006.

Primary, assisted primary, and secondary patency rates were calculated by the Kaplan-Meier method and evaluated by a log-rank test. In addition, a Cox proportional hazard analysis with properties having $P < 0.3$ in a univariate analysis was performed to determine the relative risk of each property. $P < 0.05$ was considered to be significant.

RESULTS

One hundred seventy-six patients underwent infrainguinal bypass from July 1991 to July 2005: 179 limbs and 181 autogenous vein grafts. Because the purpose of this study was to elucidate the risk factors for late graft failure (ie, graft thrombosis or stenosis requiring some revision surgery to maintain its patency and which occurred over 30 days after the initial bypass surgery), we excluded 2 grafts in 2 patients who died within 30 days of surgery and 18 grafts that occluded or required revision surgery to maintain graft patency within 30 days after the initial surgery. None of these excluded patients had taken EPA.

One hundred fifty-six patients with 161 grafts in 159 limbs were enrolled. At the final analysis, 75 grafts from 74 patients and 82 grafts from 78 patients were in the EPA and non-EPA groups, respectively.

Baseline Characteristics

The mean age of the 156 enrolled patients (116 men and 40 women) was 67.5 years (range, 26–88 years). Indications for bypass surgery were arteriosclerosis obliterans (143 [92%]), Buerger's disease (10 [6%]), remote vascular trauma (2 [1%]), popliteal artery aneurysm (1 [1%]), acute arterial occlusion (1 [1%]), and chronic arterial occlusion due to an unknown cause (4 [3%]). Infrainguinal bypass was performed for disabling claudication in 56 limbs and for critical limb ischemia in 103 limbs. The 161 grafts used for bypass surgery comprised 125 (78%) single grafts (91 reversed, 23 in situ, and 11 nonreversed vein) and 36 (22%) spliced vein grafts. The distal landing artery was the popliteal artery in 78 patients (51 above the knee and 27 below the knee) and a more distal artery in 83 (44 posterior tibial artery, 16 peroneal artery, 8 anterior tibial artery, 6 tibioperoneal trunk, and 9 pedis dorsal artery). Concomitant reconstruction for inflow improvement was performed in 25 (16%) bypasses, and 19 (12%) bypasses were repeat surgeries. Existing preoperative comorbidities included type 2 diabetes mellitus (75 [48%]), hypertension (97 [62%]), ischemic heart disease (47 [30%]), stroke (34 [22%]), and renal failure while undergoing hemodialysis (21 [13%]). Of the 154 patients with a measured preoperative serum cholesterol level, 22 (14%) had hypercholesterolemia. One hundred and fifteen (74%) patients had a history of smoking.

Effect of EPA on Graft Patency Rate

Perioperative properties of the EPA and non-EPA groups are summarized in **Table I**. There were no significant differences between the groups, except with regard to renal failure with hemodialysis (EPA, 4 [5%] vs non-EPA, 17 [21%]).

Primary, assisted primary, and secondary graft patency rates for each group are shown in **Figure 1**. The cumulative primary patency rates of the EPA and non-EPA groups were 93% and 86%, 89% and 74%, and 83% and 68% at 12, 36, and 60 months, respectively. The EPA group was significantly better than the non-EPA group in terms of primary patency ($P = 0.042$). The assisted primary patency rates of the EPA and non-EPA groups were 94% and 87%, 91% and 83%, and 84% and 80% at 12, 36, and 60 months, respectively, and the secondary patency rates of the EPA and non-EPA group were 94% and 87%, 91% and 83%, and 87% and 80% at 12, 36, and 60 months, respectively. There was no statistically significant difference between the groups in either assisted primary or secondary graft patency rate.

Effect of Other Factors on Graft Patency Rate

Based on univariate analysis, the history of ischemic heart disease, concomitant inflow procedures, and graft minimum diameter were significant risk fac-

Table I. Perioperative parameters in patients who underwent infrainguinal bypass surgery using autogenous grafts for peripheral arterial disease in a lower limb. Patients were categorized into 2 groups depending on postoperative use of eicosapentaenoic acid (EPA). Data are no. (%) except where otherwise noted.

Properties	EPA* (n = 75)	Non-EPA† (n = 82)	*P*
Age, mean (SD), y	68.5 (11.4)	67.0 (9.3)	0.409‡
>70	38 (51)	41 (50)	1.000
≤70	37 (49)	41 (50)	
Sex			0.996
Male	57 (76)	59 (72)	
Female	18 (24)	23 (28)	
Reason for surgery			1.000
Critical limb ischemia	50 (67)	54 (66)	
Claudication	25 (33)	28 (34)	
Type 2 diabetes mellitus			0.406
Yes	34 (45)	42 (51)	
No	41 (55)	40 (49)	
Hypertension			0.147
Yes	52 (69)	45 (55)	
No	23 (31)	37 (45)	
Ischemic heart disease			0.734
Yes	22 (29)	25 (30)	
No	53 (71)	57 (70)	
Stroke			0.328
Yes	15 (20)	21 (26)	
No	60 (80)	61 (74)	
Hypercholesterolemia§			1.000
Yes	11 (15)	12 (15)	
No	64 (85)	68 (85)	
Renal failure			0.047
Yes	4 (5)	17 (21)	
No	71 (95)	65 (79)	
Smoking history			0.685
Yes	58 (77)	58 (71)	
No	17 (23)	24 (29)	
Diagnosis			0.669
ASO	69 (92)	70 (85)	
Others	6 (8)	12 (15)	
Distal anastomosis			1.000
Popliteal	35 (47)	41 (50)	
More distal	40 (53)	41 (50)	

(continued)

Table I. (Continued)

Properties	EPA* (n = 75)	Non-EPA† (n = 82)	*P*
Vein graft			0.568
Single	55 (73)	66 (80)	
Spliced	20 (27)	16 (20)	
Inflow operation			0.712
Yes	14 (19)	10 (12)	
No	61 (81)	72 (88)	
Redo surgery			0.526
Yes	11 (15)	8 (10)	
No	64 (85)	74 (90)	
Graft diameter, mean (SD)§	3.5 (0.9)	3.6 (1.0)	0.424
<3 mm	26 (36)	18 (23)	0.060‡
≥3 mm	47 (64)	61 (77)	
Warfarin			0.873
Yes	37 (49)	47 (57)	
No	38 (51)	35 (43)	
Antiplatelet drug			0.828
Yes	47 (63)	59 (72)	
No	28 (37)	23 (28)	
Statin§			0.526
Yes	12 (16)	8 (12)	
No	63 (84)	73 (88)	
Continued smoking§			1.000
Yes	12 (16)	18 (22)	
No	62 (83)	64 (78)	

ASO = arteriosclerosis obliterans.
*Started oral EPA 900 to 1800 mg/d within 2 weeks of surgery and continued for ≥3 months.
†Did not administer EPA within 3 months after surgery.
‡χ^2 test.
§N values less than total are the result of missing data.

tors for primary patency ($P = 0.039$, $P = 0.015$, and $P = 0.011$, respectively). Graft minimum diameter was the only significant factor for assisted primary and secondary patency rates ($P = 0.005$ and $P = 0.004$, respectively) (**Table II**). Vein grafts with a minimum diameter visualized on postoperative angiography of <3.0 mm were significantly worse than larger vein grafts in terms of patency (**Figure 2**). The number of patients in the EPA group with a vein graft size <3.0 mm was 26 versus 18 in the non-EPA group. Patients in the EPA group

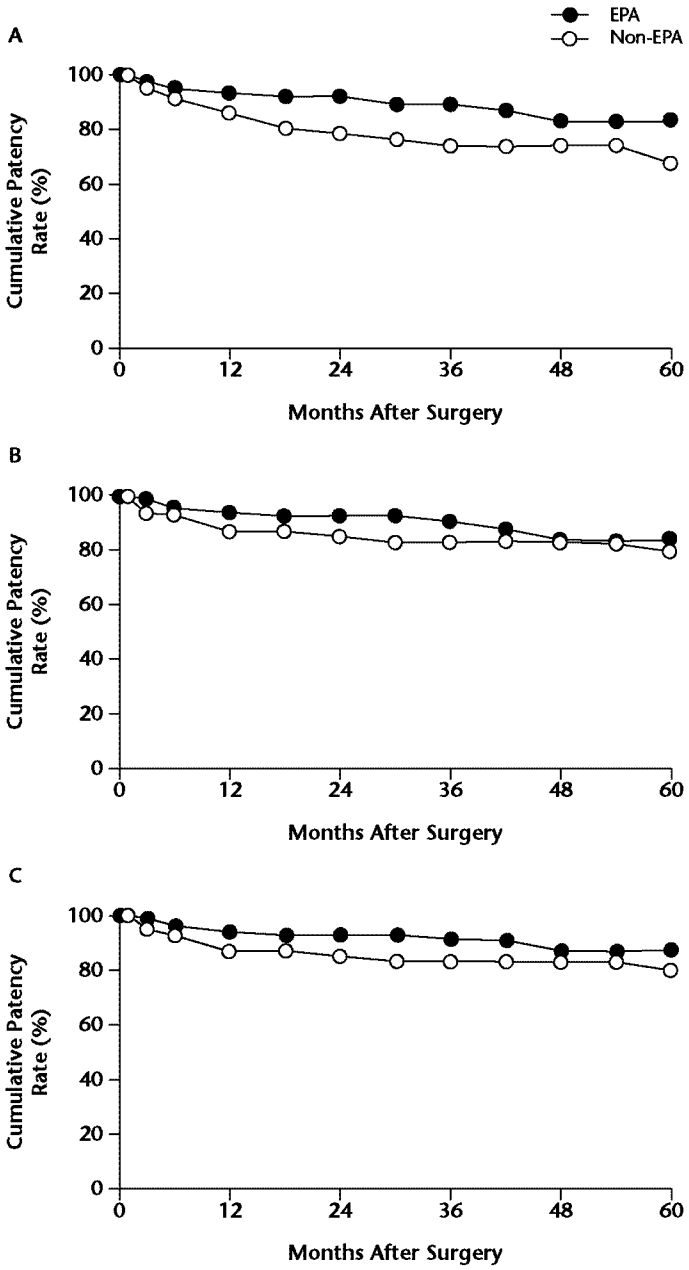

Figure 1. Primary (A), assisted primary (B), and secondary (C) patency rates of autogenous vein grafts in patients who underwent infrainguinal bypass surgery for peripheral arterial disease in a lower limb. Patients were categorized into 2 groups depending on postoperative use of eicosapentaenoic acid (EPA).

Table II. *P* Values of log-rank test to determine association between patient properties and graft patency in patients who underwent infrainguinal bypass surgery using autogenous grafts for peripheral arterial disease in a lower limb.

	Patency		
Properties	Primary*	Assisted Primary†	Secondary‡
Age	0.987	0.860	0.961
Sex	0.696	0.688	0.512
Operative indication	0.269	0.304	0.387
History			
Diabetes mellitus	0.985	0.997	0.816
Hypertension	0.613	0.967	0.814
Ischemic heart disease	0.039	0.415	0.340
Stroke	0.684	0.244	0.117
Hypercholesterolemia	0.570	0.836	0.775
Renal failure	0.612	0.241	0.211
Smoking	0.669	0.816	0.897
Diagnosis	0.821	0.349	0.308
Distal anastomosis	0.278	0.161	0.107
Used vein graft	0.681	0.593	0.681
Concomitant inflow operation	0.015	0.324	0.287
Repeat surgery	0.624	0.483	0.896
Graft diameter	0.011	0.005	0.004
Concomitant medication			
Warfarin	0.476	0.933	0.926
Antiplatelet drug	0.715	0.801	0.706
Statin	0.724	0.851	0.816
Continued smoking	0.779	0.859	0.760
Eicosapentaenoic acid	0.042	0.320	0.213

*Uninterrupted duration of patency without intervention.
†Uninterrupted duration of patency with intervention.
‡Duration of patency restored to the same conduit after bypass graft occlusion.

had better patency after 3 months than those in the non-EPA group, but the difference was not statistically significant.

Cox Proportional Hazards Analysis

Using factors for which $P < 0.3$ by univariate analysis, a Cox proportional hazard analysis was performed. For primary patency rate, graft minimum diameter and perioperative use of EPA were significant factors ($P = 0.002$ and $P = 0.004$,

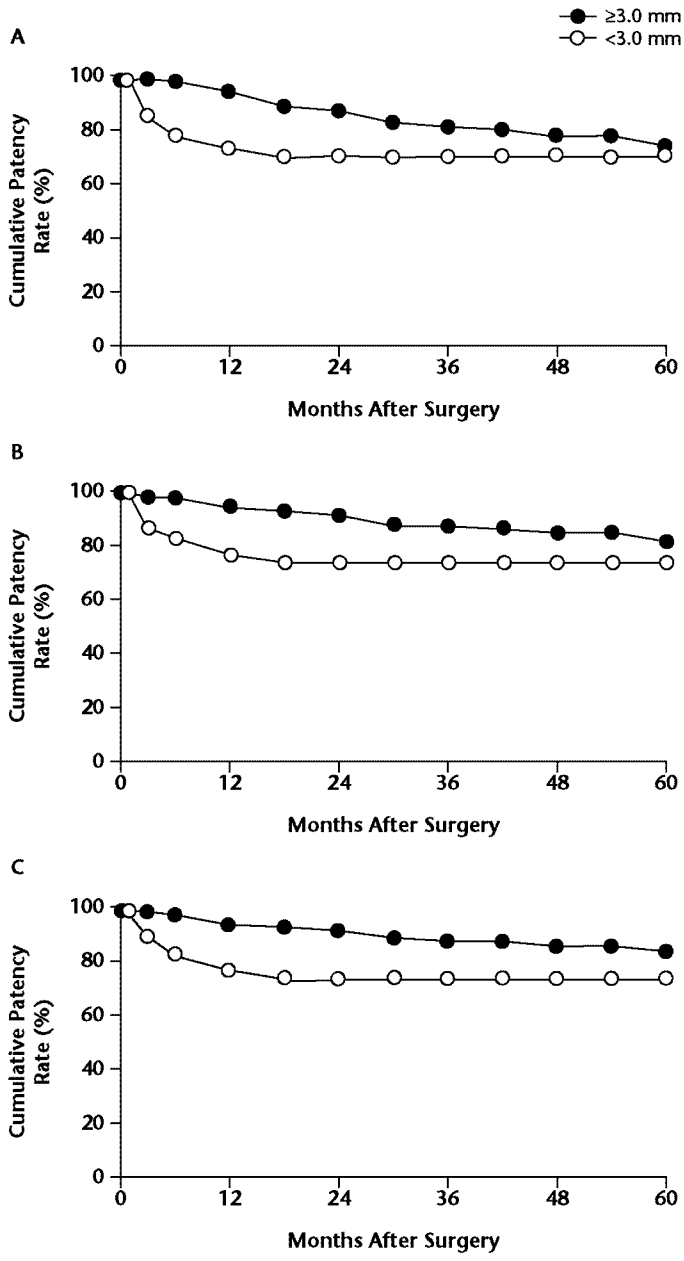

Figure 2. Primary (A), assisted primary (B), and secondary (C) patency rates of autogenous vein grafts in large (≥3 mm diameter) and small (<3 mm) veins in patients who underwent infrainguinal bypass surgery using autogenous grafts for peripheral arterial disease in a lower limb.

Table III. Results of a Cox proportional hazards analysis using factors that had $P < 0.3$ by univariate analysis.

Parameters	*P*	Risk Ratio	95% CI
Primary patency*			
Ischemic heart disease	0.226	1.661	0.730–3.775
Inflow operation	0.060	2.467	0.964–6.311
Distal anastomosis	0.797	1.108	0.507–2.422
Graft minimum diameter	0.002	0.250	0.105–0.596
EPA, perioperative use	0.004	0.282	0.120–0.665
Assisted primary patency†			
Renal failure	0.277	1.857	0.609–5.662
Stroke	0.241	0.480	0.141–1.637
Distal anastomosis	0.341	1.513	0.645–3.550
Graft minimum diameter	0.021	0.361	0.152–0.859
Secondary patency‡			
Renal failure	0.443	1.614	0.487–5.348
Stroke	0.157	0.343	0.078–1.506
Inflow operation	0.857	1.124	0.317–3.978
Distal anastomosis	0.358	1.572	0.599–4.125
Graft minimum diameter	0.003	0.204	0.072–0.577
EPA, perioperative use	0.077	0.396	0.142–1.105

EPA = eicosapentaenoic acid.
*Uninterrupted duration of patency without intervention.
†Uninterrupted duration of patency with intervention.
‡Duration of patency restored to the same conduit after bypass graft occlusion.

respectively). For assisted primary and secondary graft patency rates, graft diameter was the only significant factor ($P = 0.021$ and $P = 0.003$, respectively) (**Table III**).

DISCUSSION

Graft failure with thrombosis can occur at any time after the first postoperative month. It is usually due to the development of a flow-reducing lesion within the bypass graft or its inflow or outflow tract, and intimal hyperplasia is a prominent cause of failure and graft thrombosis. When significant intimal hyperplasia occurs in an infrainguinal graft, it usually leads to graft failure 2 to 18 months after the operation; thereafter, progression of the atherosclerotic disease process involving the inflow or outflow tract of the arterial reconstruction becomes the predominant cause of failure and graft thrombosis.[3,4] Accordingly, inhibition of intimal hyperplasia and the progression of atherosclerotic disease can improve graft patency. Although various drugs have been shown to inhibit

intimal hyperplasia in experimental models,[10–17] no drugs have been proven effective in preventing late graft failure in a clinical setting. To improve the long-term patency of infrainguinal bypass with an autogenous vein graft, many studies, mainly using antiplatelet or anticoagulant agents, have been performed. Although aspirin and dipyridamole were used in several studies, the results were controversial.[18–20] A positive result with ticlopidine on the 2-year patency of saphenous vein bypass grafts in the leg was reported by Becquemin.[21] Sarac et al[22] indicated that concomitant use of warfarin and aspirin was superior to aspirin monotherapy in patients at high risk of graft failure. The benefits of oral anticoagulant agents have been reported elsewhere.[23,24] The results from a retrospective analysis of 172 consecutive patients[25] suggested the efficacy of statins in improving secondary patency ($P < 0.02$), but not primary patency. Although the randomized, controlled study by Eritsland et al[26] reported that dietary supplementation with n-3 fatty acids reduced the incidence of vein graft occlusion in 610 patients undergoing coronary artery bypass grafting ($P < 0.004$), this has not been reported in the field of leg revascularization.

In the present study, the EPA group was significant in terms of the primary patency of the autogenous vein graft in the leg. Basic and clinical research has indicated that EPA has a positive effect on atherosclerosis as well as intimal hyperplasia. In experimental models, it was found that fish oil including EPA was associated with reduced intimal hyperplasia in injured artery and vein grafts.[27–29] Within several weeks after bypass grafting, remodeling of the implanted vein graft occurs under the influence of the arterial environment.[30] Intimal hyperplasia develops in the early period after vein grafting; therefore, the anti-atherogenic and antithrombotic actions of EPA[7,8] must function most effectively during this time. In addition, replacement of arachidonic acid with EPA in the lipopolysaccharides of the cell membrane during this early period may lead to inhibition of intimal hyperplasia and atherosclerotic change at a later time. The difference between the EPA and non-EPA groups in primary patency became more evident 6 months after bypass surgery. Possible reasons for the lack of significant differences in the assisted primary and secondary patency rates were that the observation period after revision surgery was shorter, revised lesions were localized, and >50% of patients took EPA after revision surgery.

Size,[31–36] quality,[33–36] and length of vein graft[36–38] have been indicated as risk factors affecting the long-term patency of vein grafts. In the present study, though neither quality nor length was evaluated, graft diameter was the most significant risk factor for primary, assisted primary, and secondary patency. Most of the grafts that failed (primary patency) within 6 months after bypass surgery were categorized as smaller vein grafts of <3 mm in diameter, while, as mentioned previously, most of the grafts that failed after 6 months were from the non-EPA group. This suggests that the effectiveness of EPA might be more prominent at later stages and not as obvious in the early stage.

This retrospective study design is a limitation and thus significant caution should be given in respect to its interpretation. There was no rule determining

about which patients were chosen to receive EPA after bypass surgery while others were not. Thus, there might be potential selection bias even at the starting point of the use of EPA. Data on the use of EPA was gained retrospectively from patients' records and might be incomplete and subject to recall bias. The small sample size might have been a limitation to the study. It was also impossible to evaluate patient compliance and duration of therapy. Continued use of EPA for >3 months after bypass surgery could not be followed-up in all cases and, conversely, a few patients in the non-EPA group started oral EPA >3 months after surgery. Large, multicenter, randomized, prospective trials are needed to demonstrate the true clinical efficacy of EPA.

CONCLUSION

This small retrospective study suggests the possibility of an inhibitory effect of EPA on late graft occlusion of autogenous veins in the leg. Although graft diameter was the most important factor for long-term patency of infrainguinal vein bypass grafts, the perioperative use of EPA significantly improved primary patency among these subjects.

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